Prednisone and Prednisolone in the Treatment of Rheumatoid Arthritis

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EXPERIENCE of the limitations of cortisone and hydrocortisone as therapeutic agents in the management of patients with rheumatoid arthritis has led to a search for newer and more potent compounds with fewer undesirable side effects. With the knowledge that the physiological properties of the adrenal steroids can be modified by relatively minor adjustments of their structural formulæ, a number of compounds have been synthesised and tried therapeutically. One of the earliest of these, 9α-fluoro-hydrocortisone acetate was tested by Boland and Headley in 1954, who found its anti-rheumatic activity to be about ten times greater than that of hydrocortisone, but unfortunately the drug had marked salt and water retaining properties which prevented its use as a practical method of treatment.

More recently prednisone and prednisolone have been synthesised. These two drugs are analogues of cortisone and hydrocortisone respectively, are derived from them, and differ only in having a double bond linkage between the first and second carbon atoms of the steroid nucleus. Bunim, Pechet, and Bollet (1955) were the first to describe their successful use in seven cases of rheumatoid arthritis, and since then further reports have followed confirming the effectiveness of both drugs (Dordick and Gluck, 1955; Margolis, Barr, Stolzer, Eisenbeis, and Martz, 1955; Hart, Clark, and Golding, 1955; and Boland, 1956). At present the general opinion held is that both substances possess an anti-rheumatic effect about three to five times greater than cortisone, and when employed in equivalent therapeutic dosage they have less sodium-retaining properties (Bunim, Pechet, and Bollet, 1955; and Nabarro, Stewart, and Walker, 1955). There is apparently little, if any, difference in the two drugs in respect of their usefulness or side effects (Bunim, Pechet, and Bollet, 1955), and Boland (1955) considered them interchangeable.

From these preliminary observations it seemed that these drugs were capable of modifying and suppressing rheumatic activity to an extent greater than any drug hitherto employed in the treatment of rheumatoid arthritis. For these reasons and because the majority of existing reports had been concerned with the short-term aspects of treatment, it was decided to carry out an extended trial of prednisone and prednisolone in a group of patients with severe and incapacitating rheumatoid arthritis. The object of the study was to discover—

1. The usefulness or otherwise of the drugs as a method of long-term treatment.
2. To evaluate the degree of improvement, objective and subjective, which could be achieved during treatment.

3. To discover whether long-term treatment would reveal diminishing anti-rheumatic activity previously observed to occur with cortisone and hydrocortisone.

4. To discover and assess the nature and seriousness of side effects during continued treatment.

Method.

Eleven patients with rheumatoid arthritis were treated in hospital and at a special out-patient clinic. Each was chosen for treatment because of the severity of the arthritis, or because of the failure of traditional methods to provide reasonable relief of symptoms. Initially, they were admitted to hospital, where a complete clinical examination and survey of their joints was made. Preliminary radiographs of the chest and barium meal examination of the gastro-intestinal tract were obtained in each case because of the known hazards of adrenal steroid therapy in reactivating healed pulmonary tuberculosis and producing peptic ulcers. No patient was treated who had a history of dyspepsia or who was known to have had a previous peptic ulcer.

Before starting treatment joint function was assessed. This included measurement of the circumference of the proximal interphalangeal joints (P.I.P.) with jewellers' rings; the mobility of the major joints, wrists, elbows, knees, and ankles; the maximum circumference of the knee joints; and the power of the hand grip by the patient's ability to squeeze an inflated sphygmomanometer cuff above 50 mm. of mercury. At one, three, six, and twelve months later patients were re-examined and the degree of improvement recorded as follows :—

Grip.

Each 10 mm. increase in strength was scored as one point (+1). Where a decrease was observed a negative sign was recorded.

Proximal Interphalangeal Joint Size.

Each P.I.P. joint was measured. The ring sizes go from A to Z and were numbered 1 to 26. The total score for the eight joints was recorded and the percentage increase or decrease noted at each examination.

Joint Mobility.

Each 5 degree increase in joint movement over the initial angle of movement was scored as one point. Where fibrous or bony ankylosis was present movement could not be expected to improve so that, in affected patients, only the more mobile joints were measured. Three patients had their knee-joints manipulated under anæsthesia while in hospital, but the increased joint mobility obtained was excluded from the main findings.

Knee-joint Circumference.

The maximum knee-joint circumference was measured in centimetres. Each half-centimetre (0.5 cm.) decrease in joint size was scored as –2 points. If the joint size increased a positive sign was recorded.

The Erythrocyte Sedimentation Rate (E.S.R.).

The Westergren method was adopted and the figures obtained at the examinations are shown in the results.

Stage and Grade of Arthritis.

This was assessed before treatment started and at the end of six and twelve months, and the degree of therapeutic response estimated in accordance with the recommendation of the American Rheumatism Association (Steinbrocker, Traeger, and Batterman, 1949).

The composition of the series of patients treated is given in Table 1.

TABLE 1.

Case No.	Sex	Age	Duration Arthritis	Stage	Class	Previous Drug Therapy
1. G. R.	M.	50	8 months	III	IV	Aspirin.
2. M. G.	F.	41	4 years	IV	III	Aspirin, gold, corticotrophin, cortisone, phenylbutazone.
3. M. S.	F.	38	11 years	IV	IV	Aspirin, gold, phenylbutazone.
4. T. R.	M.	64	1½ years	IV	II-III	Aspirin, phenylbutazone,
5. B. I.	F.	58	14 years	IV	III	Aspirin, gold, pregnenolone, phenylbutazone. cortisone.
6. W. A. L. S.	M.	39	10 years	IV	III	Gold, aspirin, corticotrophin, cortisone, phenylbutazone.
7. G. T.	M.	45	6 years	IV	II-III	Aspirin, gold, phenylbutazone.
8. R. J. McV.	M.	50	5 years	IV	IV	Aspirin, gold, phenylbutazone.
9. D. B.	F.	35	14 years	IV	III	Aspirin, gold, codeine.
10. L. B.	F.	49	15 years	IV	III	Aspirin, codeine, phenylbutazone.
11. J. M.	F.	62	16 years	IV	III	Aspirin, gold.

The Stage refers to severity of joint involvement. Stage I early; Stage II moderate; Stage III severe with cartilage and bone destruction, joint deformity, etc., and extra articular soft tissue lesions such as nodules. Stage IV includes criteria of Stage III together with bony or fibrous ankylosis of joints. The Class refers to the patient's functional capacity. Class I complete functional capacity to carry on usual activities. Class II capacity adequate to conduct normal activities despite handicap. Class III functional activity limited. Class IV largely or wholly incapacitated; patient bedridden or confined to wheel-chair.

Steroid Therapy.

Initially, all patients were given prednisolone, but on occasions prednisone was used instead, depending on supplies of each drug available in the dispensary. No differences in the effects of the two were observed, and for the purposes of this report the term prednisolone covers the use of both drugs. Treatment was started in each case with a standard amount of 30 mg. daily in four divided doses, irrespective of the severity or duration of the arthritis. The drug was then gradually reduced to an effective maintenance level. Usually within twenty-four hours there was noticeable subjective improvement, pain and stiffness easing, and the patient felt more cheerful. Objective changes lagged behind subjective improvement, although a distinct alteration could be recorded within a week or so of starting treatment. This was particularly noticeable with the return of strength to the patient's grip, but decreases in joint size and increases in joint movement took place more slowly and the maximum response was not obtained for several weeks.

TABLE 2.

	Number of Patients
Length of time on maximum dosage of 30 mg. Prednisolone daily.	
(a) More than 7 days (total 8 days)	1
(b) Less than 7 days	10
Length of time required to achieve maintenance levels.	
(a) Under 30 days	2
(b) 30-60 days	7
(c) More than 60 days (96 and 88 days), Cases 3 and 7	2
Maintenance dose at end of 6 months' treatment.	
(a) 7.5 mg. daily	2
(b) 10 mg. daily	7
(c) 12.5 mg. daily	2
Maintenance dose at end of 12 months' treatment.	
(a) 7.5 mg. daily	2
(b) 10 mg. daily	5
(c) 12.5 mg. daily	3
(d) 15 mg. daily	1
(N.B.—Cases 10 and 11 assessed at 11 and 10 months respectively.)	
Number of patients who had reactivation of the rheumatoid process during maintenance treatment and requiring temporary or permanent increase in prednisolone dosage.	
(a) Requiring temporary increase in dosage and able to return to previous maintenance treatment (Cases 1 and 3)	2
(b) Requiring temporary increase in dosage and permanent increase in maintenance treatment (Cases 4, 5, and 7)	3

The initial daily dose of prednisolone was continued for five or six days and then progressively reduced by 2.5 mg. on alternate days until 20 mg. was being given. It was held at this level for several days before further withdrawals were made. When the daily dose reached 15 or 12.5 mg. the patients were discharged from hospital. Treatment was always conservative, for it was decided to reduce the prednisolone as quickly as possible to lessen the risk of toxic effects, and, since the trial was primarily concerned with long-term aspects of treatment, general improvement in symptoms was aimed at and not complete suppression of rheumatoid activity.

During out-patient supervision the drug was further reduced to levels which kept the patient comfortable and allowed a resumption of work. Maintenance treatment varied between 7.5 mg. and 15 mg. a day with the majority of patients needing 10 mg. or less. In two patients (Cases 3 and 7) initial reduction in therapy was too rapid, and the recurrence of symptoms necessitated a temporary increase for a number of weeks before final maintenance treatment could be achieved. In four other patients symptoms increased when a daily controlling dose of 10 mg. of prednisolone was reduced to 7.5 mg. in an effort to arrive at the lowest possible maintenance level. Such symptoms occurring during the phase of prednisolone reduction were due to unmasking of the underlying rheumatoid process as a result of too rapid withdrawal of the drug or reducing it below the effective controlling dose, and were not the result of a real increase in rheumatoid activity. The occurrence, however, of a true reactivation was seen in five patients when they were on steady maintenance treatment. In two (Cases 1 and 3) a return to the original controlling dose was possible after a temporary increase, but in three others (Cases 4, 5, and 7) re-establishment of control could only be maintained by increasing the drug to levels higher than those given before reactivation took place. Details of the treatment employed are given in Table 2.

Results.

Clinical Assessment.

The criteria recommended by the American Rheumatism Association (Steinbrocker, Traeger, and Batterman, 1949) to classify the severity of the arthritis, and to express the degree of improvement achieved, were adopted. The patients were assessed before treatment and at six and twelve months later, and the results recorded in Table No. 3. No alteration in the stage of the arthritic process was observed, but, as is well known, this rarely occurs particularly in patients who have established joint damage of irreversible degree. For the purpose, therefore, of evaluating clinical improvement, two variables are available for comparison. Firstly, alteration in functional capacity, and, secondly, improvement in rheumatoid activity revealed by the grade of response to treatment.

Distinct improvement in functional activity was recorded in each patient at the end of six months. Two (Cases 1 and 3) improved by two classes and the remainder by one. At twelve months this improvement was maintained in all patients except in one (Case 4), where a slight but definite lessening in functional capacity was noticed. At six months nine patients showed a Grade 2 response to treatment

TABLE 3.

Case No.	Classification of Disease State: Before Treatment — Activity of Rheumatic State	Before Treatment — Stage	Before Treatment — Class	After Treatment — At 6 months — Stage	After Treatment — At 6 months — Class	After Treatment — At 12 months — Stage	After Treatment — At 12 months — Class	Therapeutic Response to Treatment — At 6 months	Therapeutic Response to Treatment — At 12 months
1. G. R.	Active	3	4	3	2	3	2	Grade 2	Grade 2
2. M. G.	Active	4	3	4	2	4	2	,, 2	,, 2
3. M. S.	Active	4	4	4	2	4	2	,, 2	,, 2
4. T. R.	Active	4	2-3	4	2	4	2-3	,, 3	,, 4
5. B. I.	Active	4	3	4	2	4	2	,, 2	,, 2
6. W.A.L.S.	Active	4	3	4	2	4	2	,, 2	,, 2
7. G. T.	Active	4	2-3	4	2	4	2	,, 3	,, 2
8. R. J. McV.	Active	4	4	4	3	4	3	,, 2	,, 3
9. D. B.	Active	4	3	4	2	4	2	,, 2	,, 2
10. L. B.	Active	4	3	4	2	4	2	,, 2	,, 2
11. J. M.	Active	4	3	4	2	4	2	,, 2	,, 2

Grade 1 therapeutic response indicates complete remission of the disease process.
Grade 2 therapeutic response indicates a major improvement.
Grade 3 therapeutic response indicates a minor improvement.
Grade 4 no improvement or progression of the disease process.

TABLE 4.

Increase in Strength of Hand Grip over Initial Reading
(each 10 mm. rise 1 point)—two hands scored together.

Case No.	1 month	3 months	6 months	12 months	Grade of therapeutic response at 12 months
1. G. R.	+30.0	+17.5	+32.5	+35.0	2
2. M. G.	+ 9.0	+ 8.5	+ 7.5	+ 3.0	2
3. M. S.	+ 2.6	+ 7.2	+ 7.5	+ 6.0	2
4. T. R.	+19.0	+10.0	+11.0	− 2.5	4
5. B. I.	+10.1	+10.7	+ 3.6	0.0	3
6. W. A. L. S.	+ 1.0	+ 3.6	+ 2.6	+ 8.5	2
7. G. R.	+ 7.3	+ 7.7	+10.3	+10.8	2
8. R. J. McV.	+ 2.0	+ 3.0	+ 2.5	0.0	3
9. D. B.	+20.5	+18.0	+10.5	+19.0	2
10. L. B.	0.0	+ 4.0	+ 0.5	0.0	2
11. J. M.	+ 6.0	+10.5	+10.5	+10.5	2
Average all Patients	+ 9.7	+ 9.1	+ 9.0	+ 8.2	

which is classified as a major improvement. In order to attain this grading the patient must show no signs of rheumatoid activity, with the exception of an elevated sedimentation rate; show resolution of articular and extra articular inflammation and reveal no signs of any new rheumatoid process. Minimal joint swelling and impairment of joint mobility associated with this swelling may, however, be present. Lesser degrees of improvement constitute a Grade 3 response or minor improvement which was shown in two patients (Cases 4 and 7). Assessment

TABLE 5.

MEASUREMENT OF FINGER SWELLING WITH JEWELLERS' RINGS
% INCREASE (+) AND DECREASE (−) BOTH HANDS.

CASE NO.	1 month	3 months	6 months	12 months	Grade of therapeutic response at 12 months
1. G. R.	− 7.0	− 2.1	− 7.0	− 0.5	2
2. M. G.	−17.8	−13.8	−19.0	−18.0	2
3. M. S.	− 8.2	− 8.2	−11.8	−11.7	2
4. T. R.	−18.1	− 8.7	− 9.9	− 2.3	4
5. B. I.	−19.0	−19.0	−11.0	− 6.6	3
6. W.A. L.S.	−11.1	−11.0	− 4.3	− 8.0	2
7. G. T.	−10.3	−12.7	−12.1	− 9.8	2
8. R. J. McV.	− 6.8	− 1.2	+ 1.2	+ 5.4	3
9. D. B.	−13.6	−18.1	− 9.0	− 2.2	2
10. L. B.	*− 5.5	−11.0	− 3.6	− 7.0	2
11. J. M.	−10.9	−12.1	−12.5	−11.5	2
Average all Patients	−11.6	−10.6	− 9.0	− 6.5	

*One hand only recorded.

at twelve months revealed a slight deterioration, with only eight patients making a major response, two (Cases 5 and 8) had a minor response, and one (Case 4) a Grade 4 response.

It is difficult to convey through these symbols what the figures actually meant to the patients in terms of improvement in their disability. Three patients who made a Grade 2 response were totally incapacitated before treatment. Case 1 was unable to turn over in bed and had to be fed. Cases 3 and 8 were severely crippled and unable to get out of bed unaided. After six months Case 1 was back at work as a foreman in the shipyard; Case 3 was undertaking some household duties and had taken a bus ride to visit her family doctor for the first time for several years; and Case 8 was able to walk a hundred yards and could ride a bicycle once more. In lesser degrees the improvement in strength, general well-being, cheerfulness, and freedom from pain in the other patients was most gratifying. In addition to

the general clinical assessment already described, specific measurement of various joint functions was carried out, details of which are to be found in Tables 4, 5, 6, 7, and 8.

Strength of Grip.

A considerable increase in strength was recorded in seven patients at the end of one month. In three others the increase was slight, while in one there was no change. When the average of all the patients is taken, the greatest improvement was observed at the end of the first month, after which there was a gradual, but definite, decline at each of the subsequent examinations. Of the four patients (2, 4, 5, and 8), who at twelve months showed a loss of strength in comparison with the findings at one month, three (4, 5, and 8) had the poorest clinical response to treatment. On the whole, improvement in the strength of hand grip correlated well with the patient's therapeutic response.

TABLE 6.

Measurement of Joint Mobility to Show Increase (+) or Decrease (−) in Movement compared with Initial Reading—(each 5° one point).

Case No.	Joints Measured	1 month	3 months	6 months	12 months	Grade of therapeutic response at 12 months
1. G. R.	Elbows	+16	+18	+20	+14	2
2. M. G.	Elbows	+ 4	+ 5	+ 3	+ 5	2
3. M. S.	Wrists Elbows Knees	+12	+10	+11	+12	2
4. T. R.	Wrists Knees	+14	+ 2	+ 8	−11	4
5. B. I.	Wrists Elbows Knees	+11	+ 7	+ 2	+ 8	3
6. W. A. L. S.	Wrists Elbows Knees	+ 1	+ 8	− 2	+ 3	2
7. G. T.	Wrists Elbows Knees Ankles	+11	+ 4	+16	+16	2
8. R. J. McV.	Knees	+ 3	+ 2	+ 1	+ 1	3
10. L. B.	Knees	−	+12	+ 9	+17	2
11. J. M.	Knees	+ 1	+ 3	0	0	2
Average all Patients		+8.2	+7.1	+6.8	+6.5	

Proximal Interphalangeal Joints.

At one month finger-joint swelling had diminished in all by 19 to 5.5 per cent. The average decrease in joint size fell during the twelve months from an initial reduction of 11.6 per cent. to 6.5 per cent. When the figures at twelve months are compared with those at one month, five patients (1, 4, 5, 8, 9) show an actual increase in joint size varying from 6.5 per cent. (Case 1) to 15.8 per cent. (Case 4). Three of these (4, 5, 8) had a poor therapeutic response, whereas two (1, 9) were classed as showing major improvement.

TABLE 7.

CIRCUMFERENCE OF KNEE-JOINT TO SHOW INCREASE (+) OR DECREASE (−) IN SIZE
(each 0.5 cm. decrease (−) two points).

CASE NO.	Before treatment measurement both joints in cms.	1 month	3 months	6 months	12 months	Grade of therapeutic response at 12 months
1. G. R.	73.0	−10	−18	− 1	+ 5	2
2. M. G.	87.7	−22	−20	−16	−18	2
3. M. S.	62.0	− 8	+ 6	−14	+13	2
4. T. R.	74.2	− 8	− 2	− 4	− 9	4
5. B. I.	81.5	+ 9	0	+ 5	− 6	3
6. W. A. L. S.	73.0	− 3	0	+ 2	+ 2	2
7. G. T.	79.0	− 6	− 8	−10	− 4	2
8. R. J. McV.	66.0	0	+ 4	+10	+10	3
9. D. B.	71.8	−12	+10	+26	+18	2
10. L. B.	77.2	+ 2	+ 2	− 1	+ 1	2
11. J. M.	67.2	− 2	+10	+10	+10	2
Overall Decrease or Increase all Patients		−60	−16	+ 9	+20	

Joint Mobility.

This increased in all patients assessed at one month, but thereafter individual patients varied, some gaining further increases while others showed a reduction. The average improvement for all patients, however, declined slightly over the twelve months of observation. The most pronounced deterioration took place in Case No. 4, but when the individual figures for the other patients are studied there is little variation between the assessments at one and twelve months.

Knee-joint Circumference.

The majority of patients, except Cases 5 and 10, showed a decrease in knee-joint circumference at one month, but at three months only four (1, 2, 4, 7) had a reduction in swelling. The overall improvement for all patients observed at one month was thus converted into an overall increase in joint size at nine and twelve

months, which may be a reflection of the additional strain imposed on these joints by the patients' greater mobility and activity. It is of interest that Case 4 and Case 5, both of whom showed a poor therapeutic response to treatment, had a reduction in knee-joint circumference at twelve months. It is difficult to explain this finding, but it may, in part, be related to increase in rheumatoid activity reducing functional use of the joint and thereby limiting swelling.

The Erythrocyte Sedimentation Rate.

The E.S.R. was 15 mm. in one hour or more in nine patients before the trial started. Of the two with a normal E.S.R., one (Case 2) was receiving a daily suppressive dose of 67.5 mg. of cortisone acetate, when the reading was made.

TABLE 8.

ERYTHROCYTE SEDIMENTATION RATE

CASE NO.	Before treatment	1 month	3 months	6 months	12 months	Grade of therapeutic response at 12 months
1. G. R.	94	24	37	10	61	2
2. M. G.	14	35	–	39	37	2
3. M. S.	25	6	–	9	15	2
4. T. R.	95	33	64	44	58	4
5. B. I.	31	22	–	40	16	3
6. W. A. L. S.	20	5	4	13	10	2
7. G. T.	28	10	–	8	9	2
8. R. J. McV.	77	3	14	34	27	3
9. D. B.	9	3	3	3	6	2
10. L. B.	65	2	18	20	17	2
11. J. M.	15	–	3	14	12	2
Average all Patients	44	14.3	20.4	21.2	24.3	

The most marked fall in the E.S.R. was seen at one month, but thereafter the average rose during the remainder of the trial from 14.3 mm. in one hour to 24.3 mm.

SIDE-EFFECTS OF PREDNISOLONE TREATMENT.

With the exception of the occurrence of peptic ulceration in one patient which is described in detail below, unpleasant side-effects of prednisolone therapy were slight and consisted of relatively trivial symptoms which the patients readily accepted in exchange for the benefits achieved by treatment (Table 9). Rounding of the face was seen in all, and was usually apparent within two-three months of starting prednisolone. Although less pronounced, it assumed the characteristic configuration seen in Cushing's Syndrome, and seemed to occur more easily with prednisolone than in those who were previously treated with cortisone. Four female patients (3, 5, 9, and 10) had facial flushing in addition to the "Cushingoid"

facies, which resembled the flushes associated with the menopause, but there was the additional complaint of a constantly hot and burning sensation. In one patient this was a troublesome feature for some months until it ceased spontaneously. It is unlikely that this symptom is related to secondary ovarian depression induced by prednisolone since Case 9 became pregnant while receiving the drug and Case 5 had had a normal menopause ten years before. It is probably the result of a direct vasomotor response induced by the drug. An increase in facial hair growth was observed in one patient (Case 5); it was of fine texture and caused no special complaint. A gain in weight was recorded in nine patients, ranging from 20 lb. to 3½ lb. One patient lost 12 lb. on a restricted carbohydrate diet, while the weight of the other patient remained unchanged. Four patients were seriously underweight before treatment started and regained their normal weight, but in

TABLE 9.

Side-Effects of Prednisolone Treatment	No. of Patients
Facial rounding	11
Facial flushing	4
Increased facial hair growth	1
Excessive gain in weight	5
Dyspepsia—negative X-ray	2
Peptic ulcer	1

five there was an excessive increase which represents a disadvantage of prednisolone therapy especially in a condition such as rheumatoid arthritis. The increased appetite induced by treatment, coupled with the metabolic effects of steroid therapy, while advantageous in wasted patients, must be carefully observed in those whose weights are normal, and excessive gains checked. No alterations in electrolyte or water metabolism were seen during the period of observation and no patient had glycosuria, hypertension or mental disturbances as the result of treatment.

Dyspepsia and Peptic Ulceration.

Hitherto the most serious complications of prednisolone therapy has been the occurrence of peptic ulceration. Bollet, Black, and Bunim (1955) observed a peptic ulcer in three out of eighteen cases treated with prednisone and prednisolone, and stated that there was no apparent relationship between the duration of treatment or total dose of the drug and the appearance of the ulcer. With this danger in view, all patients had a preliminary barium meal examination of the stomach and duodenum before starting treatment, and at intervals throughout the trial, and, with the exception of Case No. 1, no ulceration was observed. As a precautionary measure, however, patients were advised to take a modified peptic ulcer type diet, an antacid tablet between meals, and the prednisolone after food. During treatment two patients developed mild dyspepsia, but without X-ray evidence of peptic ulceration, and the symptoms subsided rapidly without additional therapy or alteration in prednisolone dosage.

In Case 1 treatment was inadvertently started thirty-six hours before the result of the barium meal examination was received in the ward. This radiograph showed the appearance of a moderate-sized ulcer crater on the posterior wall of the body of the stomach. The decision to continue prednisolone therapy was made, in spite of the risk involved, because of the severity of the arthritis, and because it was felt that the withdrawal of prednisolone in the early stage of clinical remission would have provided a severe blow to his morale. Strict anti-ulcer treatment was therefore given in addition to the prednisolone and a special watch kept on his clinical condition. One month later gastroscopy was performed by Professor H. W. Rodgers, who reported that there was no evidence, direct or indirect, of a gastric ulcer, in the area, in which a typical ulcer showed on the X-ray. A depression in the mucosa, without converging folds, was seen to be surrounded by a low wall of folded mucosa which might have accounted for the radiological appearances. Treatment was therefore continued with greater confidence, but in February, 1956, five months after treatment started, a routine barium meal revealed the presence of a symptomless duodenal ulcer. After two weeks in-patient treatment there was radiological evidence of healing and no further dyspepsia or peptic ulceration was observed during the remainder of the trial.

Discussion.

The results achieved during the trial clearly demonstrate that prednisolone is an effective suppressive agent for the treatment of rheumatoid arthritis. This was particularly evident in those patients who had previous treatment with cortisone, for it appeared that prednisolone possessed the advantage of re-establishing control of symptoms in those who were no longer responding adequately to cortisone. Two patients had greater relief of symptoms with 12.5 and 10 mg. of prednisolone when 67.5 and 50 mg. of cortisone respectively had been inadequate, and the three patients who had experience of both drugs were convinced of the superior results achieved with prednisolone. The improvement observed in strength and functional activity and freedom from pain has already been mentioned, and this was matched by objective evidence of increased joint function. Although complete suppression of rheumatoid activity was not aimed at, the majority of patients made a Grade 2 response to treatment, and this probably represents the best that can be achieved by any drug which is not curative.

The action of prednisolone is comparable with cortisone, and while its initial results may appear superior, evidence of its diminishing activity during the trial was obtained, which shows it possesses the same disadvantage of waning anti-rheumatic activity previously experienced with cortisone. This was apparent in the reactivation of the arthritic process which occurred in five patients, in three of whom additional amounts of prednisolone were required to maintain control thereafter. A similar finding was reported by Boland (1956).

Adverse reactions to prednisolone were, with the exception of peptic ulceration in one patient, mild and did not interfere with treatment. While facial rounding and flushing seem to occur more readily with prednisolone than with cortisone, the absence of hypertension and water and electrolyte disturbances is an advantage

which the newer steroids possess over cortisone and hydrocortisone. The occurrence of dyspepsia and peptic ulceration in patients receiving prednisolone had already been referred to, and from evidence available this complication warrants special attention. Boland (1956) reported dyspepsia occurring in five patients, two of whom had duodenal ulcers, in a series of thirty-two patients treated with prednisolone for periods up to nine months. In a further seventy patients changed to prednisolone after prolonged hydrocortisone treatment the incidence of dyspepsia and ulceration increased from 7 per cent. to 37 per cent. In this series one patient developed a duodenal ulcer during treatment, and satisfactory healing was achieved with no alteration of prednisolone therapy. The fact that the ulcer can be symptomless is an additional hazard and emphasises the importance of supplementing steroid therapy with a modified peptic ulcer diet, antacids, and the post-prandial administration of the drug in an endeavour to avoid this complication. Whether these measures are useful in preventing hæmorrhage or perforation is uncertain, but they certainly did not prevent the occurrence of ulceration in this patient. As pointed out in a recent leading article in the *British Medical Journal*, a controlled trial to assess the value of antacids in preventing gastro-duodenal complications is urgently needed.

Prednisolone, like cortisone, suppresses endogenous adreno-cortical activity (Nabarro, Stewart and Walker, 1955), so that it must be remembered that abrupt termination of treatment will result in symptoms of adrenal insufficiency and patients should be warned of this danger and have an adequate supply of the drug if they leave home. The importance, too, of temporarily increasing the dose during a complicating illness or operation needs stressing. If treatment has to be stopped it should be done gradually and the adrenal cortex stimulated by corticotrophin which should overlap the final doses of prednisolone.

The knowledge that prednisolone is effective in suppressing the activity of rheumatoid arthritis focuses attention on the selection of patients who are suitable for treatment. This potent drug is unnecessary when the disease is mild and responding to other well-tried measures. However, for those whose disease is progressive so that severe crippling seems to be the likely end result, it appears justifiable to use prednisolone in the hope that a remission may occur before irreversible joint damage takes place. Those most likely to benefit are in the younger and middle-age groups with severe disease of relatively recent onset and where the disease is progressive and uninfluenced by standard methods of treatment. Even in long-standing cases, however, considerable benefit may be obtained, as shown by some of the patients in this series. When the decision to undertake treatment is made the patient must be made aware of the limitations of therapy and the necessity of carrying out strictly the measures adopted for his safety.

Summary.

A clinical trial in which eleven patients were treated with prednisolone for one year is described. Measurement of joint function was made before treatment started and at one, three, six, and twelve months thereafter, and the results recorded. Improvement was most marked at one and three months, following

which a gradual deterioration took place. Nine patients showed a Grade 2 or major therapeutic response to treatment at six months, and eight remained in this category at twelve months. The occurrence of peptic ulceration in one patient, which, however, healed without alteration in the dose of prednisolone, was the only serious complication. Minor undesirable side-effects, consisting of facial rounding in all eleven patients, facial flushing in four, increased hair growth in one and excessive gain in weight in five, were observed, but did not interfere with treatment.

It is concluded that prednisone and prednisolone are effective suppressive agents in rheumatoid arthritis, and can be used beneficially for long periods in suitable patients. Both drugs possess one of the inherent defects of cortisone and hydrocortisone, and reveal in some cases a gradual decline in anti-rheumatic activity when treatment has continued for a number of months. Because these drugs appear to increase the incidence of dyspepsia and peptic ulceration, special measures designed to limit these complications should be taken routinely during their administration.

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